REMARKS

AMENDMENTS

Claims 63 to 101 were pending in the instant application. Applicants have added new claims 110 to 123. These new claims have been inserted to further define the present invention and add no new subject matter, as they are fully supported throughout the specification as originally filed. Accordingly claims 63 to 123 will be pending in the application upon entry of the amendments presented herein.

Claims 63, 71, 75, 79, 81, 89, 90, 94 and 102 have been amended to correct minor points of form and typographical errors.

Additionally claims 63, 71, 75, 81, 90, 94, and 102 have been amended by insertion of the term "having at least 70 % sequence homology to SEQ. ID. NO. 2." These amendments are fully supported throughout the specification, and do not introduce new matter. Specific support is found, for example, on page 17, last paragraph.

Claims 63 and 81 have been amended so that the last clause of these claims now reads "detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said ligand with reporter gene expression after addition of said ligand."

Claims 75 and 90 have been amended so that the last clause of these claims now reads "detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical."

Claim 71 has been amended so that the last clause of this claim now reads "detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said ligand with said signal after addition of said ligand."

Claim 94 has been amended so that the last clause of this claim now reads "detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said test chemical with reporter gene expression after addition of said test chemical."

These amendments are fully supported throughout the specification, and do not introduce new matter. Specific support is found, for example, on page 25, last paragraph, as well as, page 26, second from last paragraph.

Attached hereto as Appendix A is a marked up version of the changes made to the claims by the current amendments. No new matter has been added.

New claims 110 to 123, which are directed to Gα15 proteins with varying degrees of sequence homology to SEQ. ID. NO. 2, are fully supported throughout the specification, and do not introduce new matter. Specific support is found, for example, on page 17, last paragraph.

Amendment and cancellation of the claims are not to be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

REJECTION OF CLAIMS 63 TO 109 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejects claims 63 to 109 under 35 U.S.C. §112, first paragraph, because "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims." Specifically, the Examiner is of the opinion that "because the specification, while being enabling for a method of identifying GPCRs or ligands by using the Gα15 of SEQ. ID NO.2, does not reasonably provide enablement for a method of identifying a GPCR by using all Gα15 G proteins."

Applicants respectfully traverse the foregoing rejection on the grounds that the claimed invention is fully enabled by the disclosure in Applicant's specification. Applicants submit that the Examiner's position, in effect, imposes an additional requirement, one not contained in 35 U.S.C. §112, of a working example or examples to enable the breadth of the claims directed to the claimed methods. Applicants assert that a working example is not required to enable the breadth of the pending claims and that "there is no magical relation between the number of

representative examples and the breadth of the claims". In re Borkowski and VanVenroy, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). In fact, § 112 only requires that the "specification contain a written description of the invention, and the manner and process of making and using it".

Additionally, it is well settled that the disclosure of invention set forth by Applicants in their application must be given the presumption of correctness and operativeness by the PTO, and the only relevant concern of the PTO under the circumstances should concern the truth of the assertions contained in the application. In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also, In re Bowen, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Examiner fails to proffer any evidence to controvert the truth of Applicants' assertions in the instant specification.

The key question then, is whether it would require undue experimentation to perform Applicants' methods as broadly claimed. As the Examiner is aware, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. See In re Wands, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988).

Accordingly, it is Applicants' position that based on the teachings of the specification, which the Examiner acknowledges enables the claimed methods with the disclosed species, the ordinarily skilled artisan would be able to make and practice the claimed methods without undue experimentation. Specifically Applicants have amended the currently pending claims to explicitly recite the sequence of Gα15, as defined in SEQ ID NO. 2.

Furthermore, Applicants specification exemplifies detailed methods for making and testing stable cell lines expressing Gα15, *i.e.* to monitor the activation of any GPCR. Accordingly, the ordinarily skilled artisan at the time of the invention would be able to perform the methods taught by the instant specification, using the defined Gα15, with no more than routine experimentation.

Moreover, the Examiner has failed to present any evidence, other than conclusory statements, as to why one of ordinary skill in the art would not be able to make and use the invention, as taught in the specification, over the scope claimed.

Applicants respectfully submit that producing and testing stable cell lines expressing Gα15 protein, as taught in the instant specification, and using these to measure GPCR activation, would be routine to one of ordinary skill in the art at the time of the present invention and would not require undue experimentation.

For all the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 63 to 109 under 35 U.S.C. § 112, first paragraph. Applicants further submit that the rejection is not applicable to new claims 110 to 123.

REJECTION OF CLAIMS 63-109 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner further rejects claims 63 to 109 under § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner is of the opinion that, "the disclosure fails to describe the common attributes or characteristics that identify members of the genus" and concludes that "because the genus is highly variant, SEQ ID NO. 2 alone are insufficient to describe the genus." Applicants respectfully traverse and request reconsideration.

Applicants respectfully submit that there is sufficient written description in Applicants' specification to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by 35 U.S.C. §112, first paragraph (see M.P.E.P. 2163.02). As the Examiner is aware, the Federal Circuit has addressed the sufficiency of a disclosure in meeting the written description requirement of 35 U.S.C. §112 for claims relating to cDNAs. Specifically, the Federal Circuit stated that

> [a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a

recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus

The Regents of the University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Accordingly, it is well settled that a claim to a genus of compounds satisfies the written description requirement if the specification either defines a representative number of its members falling within the scope of the genus by disclosing the sequence or if the specification defines the structural features common to a substantial portion of the genus. It is Applicant's position that the instant specification meets the written description requirements articulated by the Federal Circuit in Eli Lilly.

The pending claims are directed to methods of identifying a G-protein coupled receptor (GPCR) for a given ligand, the method comprising, expressing a putative GPCR in a cell comprising a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2, and a second heterologous promoter operably linked to a reporter gene, in which the cell stably expresses the Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR, contacting said cell with said ligand; and detecting reporter gene expression. The claims are further directed to methods of identifying ligands, modulators and functionally profiling a test chemical with respect to a GPCR, both using a reporter gene and a signal transduction detection system.

Applicants respectfully submit that the claimed genus of Gα15 proteins of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. In particular, the instant specification teaches the structure of a representative member of the claimed class of fluorescent proteins, *i.e.*, a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2. Thus, the instant specification describes structural and functional features common to a substantial portion of the genus.

Applicants therefore respectfully submit that the Examiner erroneously states that "the disclosure fails to describe the common attributes or characteristics that identify members of the genus." Instead, the instant specification describes the structure of Gα15 proteins based on the structural features that are common to a substantial portion of the genus, *e.g.*, SEQ ID NO. 2. Thus, the instant specification satisfies the written description requirement articulated by the Federal Circuit in Eli Lilly. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

If the Examiner insists on maintaining this rejection, the Examiner is respectfully requested to present evidence or reasons why persons skilled in the art would not recognize in Applicant's disclosure a description of the invention as defined by the pending claims. Applicants further submit that the rejection is not applicable to new claims 110-123.

REJECTION OF CLAIMS 63-109 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

A. The Examiner rejects claims 63-109 under 35 U.S.C. §112 because the Examiner alleges that the term Gα15 is vague and indefinite. Applicants respectfully traverse the rejection, Gα15 is an art recognized term that a person of ordinary skill in the art would readily recognize. Solely to expedite the allowance of the present application however, Applicants have amended the claims by including a reference to the specific SEQ. ID. NO. encoding Gα15, as requested by the Examiner. Applicants accordingly request withdrawal of the rejection.

B. The Examiner rejects claims 63-109 under 35 U.S.C. §112 because the Examiner alleges that the claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. Applicants respectfully traverse the rejection. Solely to expedite the allowance of the present application however, Applicants have amended claims 63, 71, 75, 81, 90 and 94, to clarify that the detecting step, detects a change in either signal form the signal transduction

detection system, or reporter gene expression before and after ligand, or test chemical addition. Accordingly Applicants request withdrawal of the rejection.

C. The Examiner rejects claims 71-79 and 89 –90 under 35 U.S.C. §112 because the claims recite the term "substantially." Applicants respectfully traverse the rejection. Solely to expedite the allowance of the present application however, Applicants have amended claims 71, 75 and 90 by deleting the term "substantially" and replacing it with the term "normally." This amendment does not introduce new matter, and is fully supported in the specification as filed, specific support is found, for example, on page 13, lines 3 to 10. In claims 79 and 89 the term "substantially the same" has been deleted. Accordingly Applicants request withdrawal of the rejection.

D. The Examiner rejects claims 79 and 89 because the claims are confusing, since the Examiner alleges that the term "target protein" is not known. Applicants respectfully traverse the rejection on the grounds that the term "target protein" is explicitly defined in the present specification, specific support is found, for example, on page 23, lines 2 to 12, as recited below.

> The invention provides several methods for cloning or characterizing GPCRs, screening or characterizing ligands (e.g., known ligands) of GPCRs, and identifying or characterizing compounds that modulate signal transduction. For example, the invention provides a method for determining whether a "target" polypeptide is a GPCR for a given ligand. The method involves expressing a target polypeptide in a cell described herein that comprises a reporter gene construct (e.g., a construct encoding a β-lactamase reporter gene operably linked to a NFAT promoter). In this method, the test polypeptide is contacted with a chosen ligand, usually of established activity, and a change in reporter gene expression is detected. A "target" polypeptide, which is usually a GPCR, is any polypeptide expressed by a cell that can be assayed for activity using the present invention.

Accordingly, Applicants request withdrawal of the rejection of these claims.

REJECTION OF CLAIMS 63-65, 67, 81-83, 85, 89-96 AND 98 UNDER 35 U.S.C. §103(a)

A. Claims 63-65, 67, 81-83, 85, 89-96 and 98 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pausch *et al.* (U.S. Patent No. 5, 691, 188) ("Pausch *et al.*"), in view of Offermanns *et al.* (J. Biol. Chem. 270: 15175-15180) ("Offermanns *et al*").

Specifically, the Examiner is of the opinion that "[it] would have been obvious to one of ordinary skill in the art to have substituted the Gα15 protein of Offermanns *et al.* for the G-protein of Pausch *et al.* for the purposes of identifying GPCRs and ligands of said GPCRs since the use of a promiscuous G protein, such as Gα15, would produce a less specific assay wherein the artisan could easily observe any modulation of GPCRs by ligands. One of ordinary skill in the art would have been successful in using the Gα15 protein of Offermanns *et al.* in the invention of Pausch *et al.* since transfection techniques involving polynucleotides into host cells and the use of reporter genes to observe functional activity of a protein were well-known and widely successful at the time."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the one of ordinary skill in the art at the time it was made.

The pending claims are directed to methods of identifying a G-protein coupled receptor (GPCR) for a given ligand, the method comprising, expressing a putative GPCR in a cell comprising a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2, and a second heterologous promoter operably linked to a reporter gene, in which the ***cell stably expresses the Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR,*** contacting said cell with said ligand; and detecting reporter gene expression. The claims are further directed to methods of identifying ligands, modulators and functionally profiling a test chemical with respect to a GPCR, both using a reporter gene and a signal transduction detection system.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

In particular, Offermanns *et al.* neither teaches nor suggests the use of a cell line stably expressing a Gα15 protein at sufficient levels to permit promiscuous coupling to a GPCR.

The Pausch *et al.* reference does not make up for the deficiencies of Offermanns *et al.*, because Pausch *et al.* is based on the use and expression of non-promiscuous G-protein fusion proteins in yeast cells, which do not behave, or function in an analogous to the expression of promiscuous G-proteins in mammalian cells.

In support of this argument, Applicants submit the attached Declaration under 37 C.F.R. § 1.132, which serves, in part, to further differentiate the present invention from the references of record. Specifically the Declaration points out that one skilled in the art would not know whether stable expression of a Gα15 protein in a cell would be either excess and therefore cause toxicity or down regulation, or be insufficient and therefore not support promiscuous coupling. Support is provided in the attached figure entitled "Gα15 Expression Levels (Western Blot Analysis) Correlate with Promiscuous Coupling." This figure demonstrates that low levels of Gα15 expression, as shown with clone PN4-44, is not sufficient for promiscuous coupling.

These findings are of direct relevance to the Offermanns *et al.* reference cited in the Office Action, because Offermanns *et al.* does not show or teach how to generate a cell line that stably expresses Gα15, and enables promiscuous coupling of Gα15 to GPCRs. In consequence, the Offermanns *et al.* reference does provide motivation to one of ordinary skill in the art to make or use the present invention.

In the absence of the Applicants' teaching, a person of ordinary skill in the art would have had no expectation of success to create a stable cell line comprising a Gα15 protein, expressed at sufficient levels to permit promiscuous coupling to a GPCR for use in the claimed methods.

Thus the combination of references of record would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention based on the combination of references.

For all the foregoing reasons, Applicants respectfully requests that the rejection of claims 63-65, 67, 81-83, 85, 89-96 and 98 under 35 U.S.C. § 103(a) be reconsidered and withdrawn. Applicants further submit that the rejection is not applicable to new claims 110-123.

B. Claim 66 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Pausch *et al.*, in view of Offermanns *et al.*, and further in view of Abe *et al.* (J. Biol. Chem. 268: 12033-12039) ("Abe *et al.*").

Specifically the Examiner is of the opinion that "[it] would have been obvious to one or ordinary skill in the art at the time of the invention to have substituted the invention of Abe *et al.* for the G-protein-coupled receptor of Pausch *et al.* for the purpose of screening for compounds which modulate this G-protein –coupled receptor."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the one of ordinary skill in the art at the time it was made.

As discussed above, the combination of Offermanns *et al.* and Pausch *et al.* would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of

ordinary skill in the art have any expectation of success in making the claimed invention based on the cited combination of references.

The Abe *et al.* reference does not cure the deficiencies of Offermanns *et al.* and Pausch *et al.*, and does not show or teach how to generate a cell line that stably expresses Gα15, and enables the promiscuous coupling of Gα15 to a GPCR, or more specifically a taste receptor. As a consequence the cited combination does not render the claimed invention obvious. Accordingly, Applicants respectfully request withdrawal of the rejection of this claim. Applicants further submit that the rejection is not applicable to new claims 110-123.

C. Claims 68-70, 86 to 88 and 99-101 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pausch *et al.*, in view of Offermanns *et al.*, and further in view of Negulescu *et al.* (PNAS 91: 2873-7, 1994) ("Negulescu *et al.*").

Specifically the Examiner is of the opinion that "[it] would have been obvious to one of ordinary skill in the art at the time of the invention to have substituted the invention of Negulescu *et al.* for the reporter construct of Pausch *et al.* since various reporter constructs and assay systems were well-known at the time and widely successful and that the individual investigator would need to determine which reporter gene construct was most appropriate under the given experimental conditions."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the one of ordinary skill in the art at the time it was made. As discussed above, the combination of Offermanns *et al.* and Pausch *et al.* would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention based on the cited combination of references.

The Negulescu *et al* reference does not cure the deficiencies of Offermanns *et al.* and Pausch *et al.*, and does not show or teach how to generate a cell line that stably expresses Gα15, and enables the promiscuous coupling of Gα15 to a GPCR. As a consequence the cited combination does not render the claimed invention obvious.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 68-70, 86 to 88 and 99-101. Applicants further submit that the rejection is not applicable to new claims 110-123.

D. Claims 71-81, 84, 94 and 97 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Pausch *et al.*, in view of Offermanns *et al.*, and further in view of Hazlett *et al.* (Biochemistry 32: 13575-13583, 1994) ("Hazlett *et al.*").

Specifically the Examiner is of the opinion that "[it] would have been obvious to one of ordinary skill in the art to have used the fluorescent derivatives of Hazlett *et al.* in the invention of Pausch [*et al*] since the use of fluorescent dyes were well known at the time of the invention and would have given the investigators other options in the detection of GPCR-ligand interactions."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the one of ordinary skill in the art at the time it was made. As discussed above, the combination of Offermanns *et al.* and Pausch *et al.* would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention based on the cited combination of references.

The Hazlett *et al* reference does not cure the deficiencies of Offermanns *et al.* and Pausch *et al.*, and does not show or teach how to generate a cell line that stably expresses Gα15, and enables the promiscuous coupling of Gα15 to a GPCR. As a consequence the cited combination does not render the claimed invention obvious.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 71-81, 84, 94 and 97. Applicants further submit that the rejection is not applicable to new claims 110-123.

E. Claims 102-109 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Pausch *et al.*, in view of Offermanns *et al.*, and further in view of Goddard *et al.* (ISLAR 1992 Proceedings, pages 392-399) ("Goddard *et al.*").

Specifically the Examiner is of the opinion that "[it] would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Goddard *et al.* to screen a large number of cells for GPCRs or ligands as taught by Pausch *et al.* since high throughput screening assays were well known in the art at the time of the invention and one would have been motivated to use the invention of Goddard *et al.* since it was well known to the artisan that high-throughput screening assays save both time and money by increasing the efficiency of the screening process.

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the one of ordinary skill in the art at the time it was made. As discussed above, the combination of Offermanns *et al.* and Pausch *et al.* would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention based on the cited combination of references.

The Goddard *et al.* reference does not cure the deficiencies of Offermanns *et al.* and Pausch *et al.*, and does not show or teach how to generate a cell line that stably expresses Gα15, and enables the promiscuous coupling of Gα15 to a GPCR. As a consequence the cited combination does not render the claimed invention obvious.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 102-109. Applicants further submit that the rejection is not applicable to new claims 110-123.

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. Please apply any charges not covered, or any credits, to Deposit Account 50-1355.

Respectfully submitted,

Date: August 27, 2001

Lisa A. Haile, Ph.D.
Reg. No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, California 92121-2189

APPENDIX A

63. (Amended) A method of identifying a G-protein coupled receptor (GPCR) for a given ligand, the method comprising:

(i) expressing a putative GPCR in a cell, said cell comprising,

a) a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein,

(ii) contacting said cell with said ligand; and

(iii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said ligand with reporter gene expression after addition of said ligand.

64. The method of claim 63 wherein said cell comprises a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR.

65. The method of claim 63, wherein said GPCR is not naturally expressed in said cell.

66. The method of claim 63, wherein said GPCR is a taste receptor.

67. The method of claim 66, further comprising contacting said cell with a reporter gene substrate.

68. The method of claim 63, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

69. The method of claim 68, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

70. The method of claim 68, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

71. (Amended) A method for identifying a GPCR for a given ligand, the method comprising:

i) expressing a putative GPCR in a cell, said cell comprising, a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR and wherein said GPCR is [substantially] normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein;

ii) contacting said cell with said ligand; and

iii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said ligand with said signal after addition of said ligand,

wherein said signal transduction detection system comprises a dye.

72. The method of claim 71 wherein said cell comprises a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR.

73. The method of claim 71, wherein said GPCR is not naturally expressed in said cell.

74. The method of claim 71, wherein said signal transduction detection system comprises an intracellular calcium indicator.

75. (Amended) A method of a identifying of a ligand for a GPCR, the method comprising:

i) contacting a cell with a test chemical, said cell comprising

a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR and wherein said GPCR is [substantially] normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein;

ii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical,

wherein said signal transduction detection system comprises a dye.

76. The method of claim 75 wherein said cell further comprises a second heterologous promoter operably linked to a second polynucleotide encoding a GPCR.

77. The method of claim 76, wherein said GPCR is not naturally expressed in said cell.

78. The method of claim 75, wherein said signal transduction detection system comprises an intracellular calcium indicator.

79. (Amended) The method of claim 75, further comprising comparing a signal from a first plurality of cells in the presence of said test chemical with either:

i) a signal from a second plurality of cells in the presence of said test chemical, wherein said second plurality of cells lack either a promiscuous Gα protein, a target protein, or

ii) a signal from [a] said first plurality of cells in the absence of said test chemical[, wherein said plurality of cells are substantially the same as said first plurality of cells].

80. The method of claim 75, wherein said detecting comprises fluorescence detection.

81. (Amended) A method of a identifying of a ligand for a GPCR, the method comprising

i) contacting a cell with a test chemical, said cell comprising,

a) a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein;

ii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said ligand with reporter gene expression after addition of said ligand.

82. The method of claim 81 wherein said cell comprises a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR.

83. The method of claim 81, wherein said GPCR is not naturally expressed in said cell.

84. The method of claim 81, wherein said detecting comprises fluorescence detection.

85. The method of claim 81, further comprising contacting said cell with a reporter gene substrate.

86. The method of claim 81, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

87. The method of claim 86, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

88. The method of claim 81, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

89. (Amended) The method of claim 81, further comprising comparing a signal from a first plurality of cells in the presence of said test chemical with either:

i. a signal from a second plurality of cells in the presence of said test chemical, wherein said second plurality of cells lack either a promiscuous Gα protein, a target protein, or

ii. a signal from [a] <u>said first</u> plurality of cells in the absence of said test chemical[, wherein said plurality of cells are substantially the same as said first plurality of cells].

90. (Amended) A method for identifying a modulator of signal transduction in a cell, the method comprising:

a) contacting a cell with a test chemical, said cell comprising a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR and wherein said GPCR is [substantially] normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein;

b) contacting said cell with a ligand that, in the absence of the test chemical, activates signal transduction in said cell, and

c) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical.

91. The method of claim 90 wherein said cell further comprises a second heterologous promoter operably linked to a second polynucleotide encoding a GPCR.

92. The method of claim 90, wherein said GPCR is not naturally expressed in said cell.

93. The method of claim 90, wherein said signal transduction detection system comprises an intracellular calcium indicator.

94. (Amended) A method for identifying a modulator of signal transduction in a cell, the method comprising:

i. contacting a cell with a test chemical, said cell comprising,

a) a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein,

ii. contacting said cell with a test chemical; and

iii. detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said test chemical with reporter gene expression after addition of said test chemical.

95. The method of claim 94 wherein said cell comprises a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR.

96. The method of claim 94, wherein said GPCR is not naturally expressed in said cell.

97. The method of claim 94, wherein said detecting comprises fluorescence detection.

98. The method of claim 94, further comprising contacting said cell with a reporter gene substrate.

99. The method of claim 94, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

100. The method of claim 99, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

101. The method of claim 94, further comprising contacting said cell with phorbol

myristate acetate or an analog thereof.

102. (Amended) A method of functionally profiling a test chemical comprising the steps of.

i. contacting a panel of cells with a test chemical, said panel of cells comprising, a plurality of cell clones, each cell clone comprising

a) a GPCR,

b) a first heterologous promoter operably linked to a first polynucleotide encoding a Gα15 protein having at least 70 % sequence homology to SEQ. ID. NO. 2,

c) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR, wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and wherein each cell clone differs only with respect to the GPCR that is expressed,

ii. contacting said cell clones with a test chemical;

iii. detecting reporter gene expression from said cell clones

iv. comparing reporter gene expression between said cell clones.

103. The method of claim 102 wherein said cell clone comprises a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR.

104. The method of claim 102, wherein said GPCR is not naturally expressed in said cell.

105. The method of claim 102, wherein said detecting comprises fluorescence

detection.

106. The method of claim 102, further comprising contacting said cell with a reporter gene substrate.

107. The method of claim 102, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

108. The method of claim 107, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

109. The method of claim 107, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

Please add new claims as below.

--110. The method of claim 63, wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2.

124. The method of claim 71, wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2.

125. The method of claim 75, wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2.

126. The method of claim 81, wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2.

127. The method of claim 90, wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2.

128. The method of claim 94, wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2.

129. The method of claim 102, wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2.

130. The method of claim 63, wherein said Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2.

131. The method of claim 71, wherein said Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2.

132. The method of claim 75, wherein said Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2.

133. The method of claim 81, wherein said Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO:. 2.

134. The method of claim 90, wherein said Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2.

135. The method of claim 94, wherein said Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2.

136. The method of claim 102, wherein said Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2.--